EXHIBIT 90

Establishment Inspection Report	FEI:	2244683
Actavis Totowa LLC	EI Start:	07/10/2006
Little Falls, NJ 07424-5608	EI End:	08/10/2006

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SUMMARY

This inspection of a pharmaceutical manufacturer was conducted as part of the NWJ-DO FY06 Drug Work Plan under FACTS Assignment # 3474850, Operation ID # 2780701. The inspection provided general GMP coverage as well as pre-approval [redacted]. Inspectional guidance was afforded through Compliance Program Guidance Manuals 7356.002: Drug Manufacturing Inspection and 7346.832: Pre-Approval Inspections/Investigations.

The previous inspection of 1/10/2006 et. al., provided follow-up GMP coverage and surveillance coverage of the Postmarketing Adverse Drug Experience Reporting system as requested by the Center for Drug Evaluation and Research, Surveillance Program Team/Division of Compliance Risl Management and Surveillance, Office of Compliance. Significant deficiencies were observed regarding the PADE reporting system. Deficiencies were also observed regarding the GMP Quality

System. Firm management promised corrections and a written response within 10 days to the New Jersey District. The inspection was classified OAI for PADE reporting and VAI for GMPs.

The Quality, Production, Laboratory Control and Materials Systems were covered during the current inspection. Limited coverage was also provided to the Facilities & Equipment System as necessary, but this system was not covered in its entirety. An FDA 483, Inspectional Observations, was issued at the closeout meeting regarding deficiencies in the areas of Quality Control, laboratory records, OOS and production investigations, cleaning validation, bulk stability testing, detection and documentation of OOS results, sampling documentation, equipment qualification, calibrations and preventive maintenance, rejected materials and storage of components. In addition, a discussion was held with management regarding the labeling of laboratory glassware and stability of solutions. Corrections were promised for all observations and discussion items. Corrections to the previous PADE inspection will be verified under a separate assignment.

ADMINISTRATIVE DATA

Inspected firm:	Actavis Totowa LLC
Location:	101 E Main St Little Falls, NJ 07424-5608
Phone:	(973) 890-1440
FAX:	
Mailing address:	101 E Main St Little Falls, NJ 07424-5608
Dates of inspection:	7/10/2006, 7/11/2006, 7/12/2006; 7/13/2006, 7/14/2006, 7/18/2006, 7/19/2006, 7/20/2006, 7/21/2006, 7/25/2006, 7/26/2006, 7/31/2006, 8/1/2006, 8/10/2006
Days in the facility:	14
Participants:	Kristy A. Zielny, Investigator Nancy L. Rolli, Investigator

On 7/10/06, I, Investigator Kristy A. Zielny, presented my credentials and issued an FDA 482, Notice of Inspection, to Mr. Jasmine Shah, Vice President, Regulatory and Quality Compliance. Mr. Shah stated he was authorized by Mr. Divya Patel, President, to receive the Notice. A "Resources for FDA Regulated Businesses" form was also presented at this time. I explained that the purpose of my visit was to provide pre-approval [redacted] as well as GMP inspectional coverage.

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On 7/12/06, we, Investigator Kristy A. Zielny, and Investigator Nancy Rolli presented our credentials and issued a second FDA 482, Notice of Inspection, to Mr. Divya Patel, President and CEO. Investigator Nancy Rolli joined the inspection on this date.

Mr. Jasmine Shah provided all requested information and documentation as requested and arranged meetings with additional personnel as necessary.

Documentary Sample #359776, which demonstrates the interstate shipment of Hydroxyzine Hydrochloride Tablets, USP 50 mg, Batch # 5519A, was collected during the course of this inspection. An Affidavit (Form FDA 463a) was signed on 8/10/06, by Mr. Jasmine Shah, which explained the documents provided with respect to the interstate shipment of Batch # 5519A.

Labeling for all products was also collected during this inspection and is attached as **Exhibit 1.**

On 8/10/06, an FDA 483, Inspectional Observations, was issued to Mr. Divya Patel, President. In addition, a discussion was held with management both during the inspection and again at the closeout meeting. Corrections were promised for all observations and discussion items. A written response to the 483 observations was promised as well.

Investigator Zielny was present for each day of the inspection. Investigator Rolli was present on 7/12-14, 18-20, 31/06 and 8/10/06. All sections of this report are written by Investigator Zielny unless otherwise indicated. FDA 483 points 1, 2a, 2d, 2g, 3e, 5, 8, 9, 10 and 13 were written and discussed by Investigator Rolli. FDA 483 Observations 2b, 2c, 2e, 2f, 3a, 3b, 3c, 3d, 4, 6, 7, 11, 12, 14, and 15 were written and discussed by Investigator Zielny. "We" refers collectively to Investigator Rolli and Investigator Zielny. "I" refers to Investigator Zielny unless otherwise indicated.

HISTORY

Actavis Totowa LLC currently consists of two sites. This site, located at 101 East Main Street, Little Falls, NJ, is responsible for all manufacturing and testing as well as raw material receiving. The second site is located at 4 Taft Road, Totowa, NJ, and is responsible for all packaging, labeling, distribution, packaging component receiving and R&D. Actavis Totowa LLC is in the process of expanding its operations and a third site, located at 900 Riverview Drive, Totowa, NJ, is expected to begin manufacturing operations within the next 60 days.

This site, previously operating as Amide Pharmaceutical, Inc. was founded in 1983 and was acquired by Actavis on July 27, 2005. The name legally changed to Actavis Totowa LLC on May 15, 2006.

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Actavis Totowa LLC is a wholly owned subsidiary of Actavis Group, which was founded in 1956 and is based in Reykjavick, Iceland.

All regulatory correspondence should be addressed to Mr. Divya Patel, President of Actavis Totowa LLC, at 101 East Main Street, Little Falls, NJ 07424. Mr. Divya Patel is the most responsible individual at this facility, which is also the current headquarters for Actavis Totowa LLC. Mr. Sigadur Olaffson, President of Actavis U.S. Operations should also be copied on all correspondence at at 900 Riverview Drive, Totowa, NJ

This facility currently operates [redacted] on Saturdays from [redacted] Monday through Friday. There are approximately [redacted] employed at this facility. This site consists of two buildings: Building A is [redacted] and consists of administration, manufacturing, QA, QC, RA, and warehouse. Building B is approximately [redacted] and is primarily for warehousing. The floor plan of the manufacturing facility at Little Falls is attached as **Exhibit 2.**

[redacted]

The annual volume of sale for Actavis Totowa LLC, was estimated to be [redacted] Mr. Divya Patel estimated the volume of sale for this year will be approximately [redacted] million. Products manufactured at this facility include Hydrocodone Bitartrate and Homatropine Methylbromide Tablets, Hydromorphone Hydrochloride Tablets, Meperidine Hydrochloride Tablets, Oxycodone Hydrochloride Tablets and Prenatal Vitamins.

INTERSTATE COMMERCE

Mr. Jasmine Shah stated approximately [redacted] the business is conducted interstate. Products that are manufactured at 101 East main Street, Little Falls, are packaged, labeled at and distributed from the 4 Taft Road, Totowa facility.

JURISDICTION

Actavis Totowa LLC is a large generic pharmaceutical manufacturer. The Little Falls facility is responsible for raw material receiving, all manufacturing and testing of drug products. Dosage forms manufactured at this facility include prompt release tablets and capsules and extended release tablets. A complete list of products manufactured at the Little Falls facility was provided and is attached as **Exhibit 3.**

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Mr. Jasmine Shah accompanied us throughout the inspection and arranged for meetings with additional individuals as necessary. Individuals who provided information throughout the inspection include the following:

Mr. Divya Patel, President and CEO
Mr. Ashok Nigalaya, Senior Vice President, Scientific Affairs
[redacted]
Satish Laroia, Director of Manufacturing Compliance
[redacted]
Manoj Patel, Director of Engineering
Kirit Patel, Director Analytical Development Laboratory
Sigadur Oli Olafsson, President U.S. Operation
Dan Bitler, QA Director
Erick Cardona, Manager Manufacturing
Leroy Lundner, Associate Director Quality Compliance
Elina Novikov, QC Manager
Bharat Rana, Supervisor
Chandu Patel, Supervisor
Nilesh Patel, System Manager
Dimitry Kalika, IT Manager
Piyush Patel, IT Associate
Keshav Patel, QC Documentation Clerk
Bakul Shah, Chemist
Yamal Bhagat, Chemist
Girish Upadhyay, Chemist
Devendra Shah, Chemist

The following are the key officials of Actavis Totowa LLC:

Mr. Divya Patel, President and CEO
Mr. Divya Patel is the most responsible individual at the Little Falls facility as well as the Totowa site. His responsibilities include overall operations, sales, marketing and all other business aspects.

Mr. Ashok Nigalaya, Senior Vice President, Scientific Affairs

Mr. Nigalaya is the most responsible individual with respect to the scientific aspects of the business. His responsibilities include overseeing all of the laboratory, manufacturing and technical support.

Mr. Apurva Patel, Project Management, Research and Development
Mr. Apurva Patel is located at the 4 Taft Road, Totowa facility. His responsibilities include Product Development.

[redacted] is responsible for overseeing all manufacturing operations.

Mr. Satish Laroia, Director of Manufacturing Compliance
Mr. Laroia is responsible for Batch record reviews, calibration, Batch control, cGMP training and safety training.

Mr. Deepak Bhalla, Director of Technical Affairs
Mr. Bhalla is located at the 4 Taft Road, Totowa facility. His responsibilities include research and development, special projects and difficult formulations.

[redacted] is responsible for overseeing all quality control operations for raw materials, finished products and stability products.

Mr. Ashesh Dave, Director of Packaging and Labeling
Mr. Dave is located at the 4 Taft Road, Totowa facility. He is responsible for overseeing all packaging and labeling operations.

[redacted] responsible for overseeing all regulatory affairs and quality compliance issues.

Mr. Bharat Patel, Vice President Materials Management
Mr. Bharat Patel is responsible for all purchasing for the Actavis Totowa facilities.

Mr. Manoj Patel, Director of Engineering
Mr. Manoj Patel is located offsite and is responsible for HVAC, facility designs, and all utilities.

Mr. Kirit Patel, Director Analytical Development Laboratory
Mr. Kirit Patel is located at the 4 Taft Road, Totowa facility. He is responsible for method development and ANDA submissions.

Mr. Devji Kumbhani, Director of Product Formulations
Mr. Kumbhani is located at the 4 Taft Road, Totowa facility. He is responsible for the development of new products.

Mr. Apurva Patel, Mr. Rick Dowling, Mr. Satish Laroia, Mr. Frank Carlucci, Mr. Ashesh Dave, Mr. Jasmine Shah, Mr. Bharat Patel, Mr. Manoj Patel, Mr. Kirit Patel and Mr. Devji Kumbhani all report to Mr. Ashok Nigalaya, Senior Vice President, Scientific Affairs. Mr. Deepak Bhalla and Mr. Ashok Nigalaya report directly to Mr. Divya Patel, President and CEO. Mr. Divya Patel reports to Mr. Sigadur Olaffson, President of Actavis U.S. Operations. Mr. Sigadur Olaffson reports to Mr. Robert Weissman, CEO of Actavis Worldwide.

An organizational chart was provided and is attached as **Exhibit 4.**

The most responsible individual at this site is Mr. Divya Patel, President and CEO. All regulatory correspondence should be addressed to his attention at 101 East Main Street, Little Falls, NJ 07424.

CHANGES IN OPERATIONS AND PERSONNEL

There have been no changes in operations or personnel since the previous inspection of January 2006.

MANUFACTURING CODES

Manufacturing codes were explained to be assigned as follows:

The [redacted] indicates th[redacted]. The followi[redacted]re a [redacted] representing the number [redacted] dicate this was th[redacted] manufactured in that particular year). The following character is a letter indicating if the Batch was divided by different logos or customers ("A" would indicate the first logo or customer and "B" would indicate the second). The last digit would be indicative of the packaging [redacted] represent the first packaging configuration [redacted] the second).

COMPLAINTS

Complaints were reviewed during this inspection. No noted deficiencies or trends were observed.

INSPECTIONAL COVERAGE

The Quality, Production, Laboratory Control and Materials Systems were covered during the current inspection. Limited coverage was also provided to the Facilities & Equipment System as necessary, but it was not covered in its entirety. A review of the firm's manufacturing and laboratory records revealed a lack of assurance that all laboratory and manufacturing deviations are documented. See FDA 483 Observations 1-15.

Items reviewed during this inspection include, but were not limited to:

Facility Tour
[redacted]
Development Report
Regulatory Correspondence
Standard Operating Procedures (SOPs)
Receiving and Warehousing Procedures
Equipment Cleaning and Usage Logs
Equipment Calibration and Preventive Maintenance
Analytical Raw Data (raw material, finished product, stability)
Batch Records (masters and executed)
OOS Investigations
Production Investigations
Rejected Batches
Deviations and Investigations
Change Controls
Complaints
GMP Training
Equipment Qualifications
Cleaning Validations
Recovery Studies
Process Validations
Hold Time Studies

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Method Validations
Stability Data
Laboratory Notebooks
TotalChrom Data Acquisition System

[redacted] are indicated for use as an [redacted] The product has anticholinergic and antihistaminic effects. The supplier of the active pharmaceutical ingredient (API) [redacted]

The CMC section of the application was reviewed as well as the development report, raw analytical data for raw materials, in-process samples, finished product, and stability samples, method validations, the executed Batch record, equipment qualifications, calibrations and preventive maintenance, and cleaning logs. Please see Observations 3D, 6D, 7, 10, 11, 12 for deficiencies related to Benztropine Mesylate Tablets 2 mg Exhibit Batch # RBR-2137.

I explained that a recommendation of "Withhold" was to be submitted with respect [redacted]

LABORATORY

The laboratory at Actavis Totowa, LLC, Little Falls houses approximately 30 HPLCs working on the [redacted] data acquisition system. The system was changed from [redacted] approximately one year ago. This system can be accessed throughout the laboratory and is password protected. Mr. Peter Baricevic, Product Support Specialist, Informatics Service and Support, of PerkinElmer Instruments visited the Activis Totowa, Little Falls facility to answer questions and provide information regarding the functions and audit trail capabilities of the [redacted] system on 7/20/06.

The firm's current [redacted] allows analysts to abort an Analysis without leaving an audit trail. The system also does not automatically print all raw data. Analysts can change method parameters and print results in "graphic editor mode" without saving all test parameters. See Observations 2 and 4.

There are approximately [redacted] the Quality Control Laboratory. A list of employees in the QC Laboratory was provided and is attached as **Exhibit 5.** Mr. Divya Patel, President and CEO, explained that it has been extremely difficult to find qualified analytical chemists. Mr. Patel stated that Actavis advertises in the Bombay paper for employment opportunities at this facility.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Present for the closeout meeting were:
Mr. Divya Patel, President and CEO
Mr. Jasmine Shah, Vice President of Regulatory and Quality Compliance
Mr. Rick Dowling, Director of Manufacturing Operations
Mr. Dan Bitler, QA Director
Ms. Elina Novikov, QC Manager
Mr. Nilesh Patel, System Manager

Observations listed on form FDA 483

QUALITY SYSTEM

OBSERVATION 1

The quality control unit lacks authority to fully investigate errors that have occurred.

Specifically, there is no assurance that the Quality Unit can be relied upon to fulfill its responsibilities to assure that all drug products released to the marketplace meet the requirements for identity, strength, quality, and purity that they purport to have. Batches of drug products that initially failed to meet release specifications were released into interstate commerce without being fully investigated, all laboratory data was not included with the batch records and manufacturing deviations were not always documented.

Reference: 21 CFR 211.22(a)

Supporting Evidence and Relevance:
The Quality Unit and Senior Management failed to provide adequate oversight and did not fulfill their responsibilities to ensure that all data was reviewed and laboratory deviations were investigated

and resolved prior to release of drug products into commercial distribution. The Quality Unit failed to review electronic data and laboratory raw data as part of batch release and review computer audit trails. Laboratory failure investigations were inadequate, not all testing was documented in laboratory notebooks, raw data from all tests conducted were not printed, manufacturing deviations were not always documented, equipment qualifications and cleaning validation studies were inadequate and the firm failed to identify and control rejected materials. Additional examples regarding the failure of the Quality Unit to provide adequate oversight are included in FDA-483 observations 2 through 15.

Discussion with Management:

All present at the closeout meeting agreed with this Observation. Mr. Divya Patel stated that an additional three people were to be hired in Quality Assurance. The positions are for Validation/Qualification, Manager of QA Documentation and review of data, and Director of QA. Two supervisors are also to be hired in the QC Laboratory, as well as a Regulatory Affairs Specialist. For additional corrective actions please see each following Observation.

OBSERVATION 2

Laboratory records are deficient in that they do not include a complete record of all data obtained during testing.

Specifically, the Quality Unit failed to assure that laboratory notebooks include all data generated during testing and that analysts document in their laboratory notebook all sample preparation and testing at the time it occurs. Additionally, SOP QC-59 Investigation of out of specification test Results (OOS) is not always followed. For example:

a) On 1/11/06, during content uniformity testing of Ursodiol Capsules, Batch 51083A, the analyst noticed that the first two capsules were out of specification and he aborted the run. The audit trail for the laboratory data acquisition system does not indicate that the run was aborted and the analyst did not print the sample results or report the failing results in the laboratory notebook. An investigation was initiated and it concluded that a sample dilution error was made. A review of the lab notebook shows the sample dilution value in the laboratory notebook was over written, without being signed and dated as required. Additionally, a review of the laboratory notebook page showing the sample preparation and a photocopy of the same page in the investigation report, revealed that they were not the same. Changes were made in the laboratory notebook after is was signed and approved.

b) The original result of 66.5% for Sample 1-1 for pooled dissolution of Oxycodone and Acetaminophen Capsules Batch # 5259A was not documented in [redacted] and was not attached to the hard copy chromatograms. An additional injection was made for Sample 1-1 within the same chromatographic run and was used in the calculations. The original result had not been invalidated.

c) The original result of 77.7% for Capsule-2 dissolution sample for Amidrine Capsules, Batch # 5637A, was not documented in [redacted] An additional injection was made for Capsule-2 within the same chromatographic run and was used in the calculations. The original result had not been invalidated.

d) Quinapril Batch # 60423A was tested on 5/31/06 and failed to meet the specification for impurities. A new sample preparation was prepared and the batch was retested within the same chromatographic run, without prior approval as required. The original results and the results of the new sample preparation appear together in the laboratory notebook not one after the other. The out of specification (OOS) results for high impurities were invalidated without any scientific justification and the batch was retested and released. This same batch had a low yield due which was attributed to compression problems. The entire batch was compressed below the action limit for hardness, which resulted in the rejection of approximately 50,220 broken tablets, or 4.25 % of the batch.

e) The original result of 89.9% for Assay-1 in the analysis of Busnirone HCl 5 mg Tablets Batch # 3144A, 24 month stability was not documented in [redacted] An additional injection was made for Assay-1 within the same chromatographic run and was used in the calculations. The original result had not been invalidated.

f) There was no notation in [redacted] although the original result for Assay-1 of Amidrine Capsules Batch # 5113A did not show any peaks (due to injection of the wrong vial). An additional injection was made and results were recorded without documenting the discrepancy. A note was later squeezed into the Laboratory Notebook just above the "Conclusion" section of the analysis.

g) On 10/7/05 during the testing of Hyoscyamine Sulfate Tablets, Batch 5823A, one assay value was approximately double the expected value. The failing results were attributed to a transcription error in the sample weight. The failing results were not recorded in the laboratory notebook and were not printed from the laboratory data acquisition system.

Reference: 21 CFR 211.194(a)(4)

Supporting Evidence and Relevance:

2a) **Exhibit** 6, page 4 of Investigation # 06-001 states that on 1/11/06, during content uniformity (C.U.) testing of Ursodiol Capsules lot 51083A, the analyst saw the Ursodiol responses for the first two samples were more than 33% higher than the standard and he stopped the run, saw the dilution error and notified the supervisor. I explained that the analyst should not have aborted the run because the first two samples were out of specification. Furthermore, the [redacted] data acquisition system (TurboChrom) in use at Actavis does not show on the audit trail that the run was aborted. I further explained that it would be easier to support the dilution error theory if all ten capsules would have been tested. Instead the run was aborted after two capsules failed to meet specifications and the failing raw data was never recorded in the laboratory notebook (**Exhibit 7**) and the raw data was not printed from the laboratory data acquisition system. The batch was released based on the passing retest results. I stated that all data, both passing and failing should be documented in the laboratory notebook.

Exhibit 7, page 4 of the Laboratory Notebook dated 1/11/06, shows that the dilution value used to test the batch was 150.0 ml, which would have been correct, but it was overwritten with an arrow to look like 50.0 ml, which is incorrect. **Exhibit 6**, page 13, a photocopy of the laboratory notebook page, included with the investigation is different from the laboratory notebook (**Exhibit 7 page 4**). Someone went back and changed the dilution value in the notebook after it was reviewed. The photocopy of the notebook included with the investigation was not overwritten. No one at the firm

could explain why the notebook page and the photo copy of the same notebook page were not the same. Included as **Exhibit 8 page 7**, is a copy of the Ursodiol test method.

2b) In reviewing the chromatograms for the pooled dissolution release testing of Oxycodone and Acetaminophen Capsules Batch # 5259A, I noted that there were two injections made during the same chromatographic run for Sample 1-1 on 4/14/05 (**Exhibit 9**). The original result for Sample 1-1 was 65.5% Oxycodone dissolved (**Exhibit 10**). This result was not recorded in Notebook # 700-34 (**Exhibit 11**) nor was an investigation initiated into the low result. The second injection made for Sample 1-1 resulted in [redacted] (**Exhibit 12**) and this was the result that was reported on page 244 of [redacted] (**Exhibit 11, page 5**). Also on page 244 is a note that states, "Due to one time artifact on the injection # Sample 1-1 out of two, may be due to contamination from the vial. Inform supervisor 'NP' as per his instruction rechromatographed the same solution in the new vial. The contamination [is] not seen in the chromatogram." The original vial had not been re-injected. The original results had not been invalidated and no investigation was written until 7/19/05 (**Exhibit 13**). The investigation consisted of a "Note to File" and states that although "the supervisor had attributed the lower oxycodone value to a contamination of the autosampler vial, … this explanation appears unlikely, since contamination would have been expected to give higher or extraneous peaks in the chromatogram. Based upon the evidence, this was not the case, since lower peak areas were seen with no extraneous peaks in the same chromatogram." I explained that the original result should have been reported and investigated at the time it had occurred. I also explained that laboratory notebooks should reflect all results received; not just acceptable results.

2c) In reviewing the chromatograms for the dissolution testing of Amidrine Capsules, Batch # 5637A, I noted there were two injections made in the sequence which were identified as Capsule-2 (**Exhibit 14**). The original result of 77.7% for Capsule-2 (**Exhibit 15**) was not documented in Laboratory Notebook # 349-08 (**Exhibit 16**). The second injection made for Capsule-2 (**Exhibit 17**) was not a re-injection of the original vial, and was used in the calculations. The original result had not been invalidated. The "Note to File" referred to the original injection for Capsule-2 in stating "it appeared that this value was an aberration" and "no obvious reason could be seen for the aberration" (**Exhibit 18**). I explained that the original results should have been documented in the Laboratory Notebook and an investigation should have been initiated starting with the re-injection of the same sample vial.

2d) Page 4 of **Exhibit 19**, Investigation # 06-029 for Quinapril/Hydrochorthiazide tablets, Batch 60423A states the batch initially failed to meet impurity specifications on 5/31/06. The largest unknown peak [redacted] which is greater than the specification of [redacted] The analyst noticed the sample was failing prior to the run finishing, so he made a new sample preparation and ran a second sample within the same chromatographic run. The supervisory approval for the second sample preparation was not documented until the following day (6/1/06). Procedure QA-059 requires a supervisory approval before a retest is performed (Exhibit 33).

I explained the importance of letting the chromatographic run finish and then performing a documented investigation after all test methods and results are evaluated. At that point a decision can be made as to whether a second sample preparation should be prepared and tested. Page 5, of exhibit # 19, Investigation 06-029, states that the problem was traceable as a laboratory error and the results were disqualified. Included as **Exhibit 20**, are th[redacted]data acquisition sheets. There is no data to support this conclusion. An additional eight samples were tested, met specification and the batch was released. Included as **Exhibit 21**, is the test method for Quinapril/Hydrochorthiazide.

There is no assurance that this lot meets all specifications for purity as results were invalidated without any data to support the conclusion of laboratory error. The batch fell below the yield specification, which was attributed to compression problems. Furthermore, the entire batch was compressed below the action limit for hardness, which resulted in the rejection of approximately [redacted]h (**Exhibit 86**).

2e) In reviewing the chromatograms for the assay analysis of Buspirone HCl 5 mg Tablets Batch # 3144A, 24 month stability, I noted that two injections were made in the same sequence for Assay-1(3144A-500 Pack) on 3/19/05 (**Exhibit 23**). The original result of 89.9% for Assay-1 (**Exhibit 24**) was not documented in Laboratory Notebook # 666-01 (**Exhibit 25**). The second injection for Assay-1 (**Exhibit 26**) was used in the calculations and the original result had not been invalidated. The "Note to File" was written on 7/15/05 to attempt to explain the reason for the second analysis. The Note indicated "examination of the autosampler vial showed the septum [was] not seated properly. This could give an errant injection..." (**Exhibit 27**). I inquired as to how the analyst would remember the exact circumstances of an event that occurred four months earlier. The response was that this is what the analyst stated and that is what was documented. I indicated that an investigation should have been initiated at the time of the occurrence in order to immediately identify an assignable cause if one was present. I also indicated that all results should appear in the Laboratory Notebook, not only retest results once they are found to meet specification.

2f) In reviewing the chromatograms for the assay testing of Amidrine Capsules Batch # 5113A, I noted that Assay-1 was run twice on 3/4/05 (**Exhibit 28**). There was no notation in Laboratory Notebook # 349-07 although the original result for Assay-1 of Amidrine Capsules Batch # 5113A did not show any peaks (**Exhibit 29**), which was due to the injection of the wrong vial as indicated in a "Note to File" on 7/18/05 (**Exhibit 30**). The second injection results were recorded without documenting the discrepancy. A note was later squeezed into the laboratory notebook just above the "Conclusion" section of the analysis (**Exhibit 29, page 5**). I explained that the original result should have been recorded in the laboratory notebook at the time the analysis was made and that an investigation should have been initiated at that time. I explained that under no circumstances, should information be added later to the laboratory notebook such as was done in squeezing a note in above the conclusion section in this example.

2g) There is no assurance that all raw data files are printed and that all testing is documented in the laboratory notebooks. On 10/7/05, during the testing of Hyoscyamine Sulfate Tablets, Batch 5823A,

one assay value was approximately double the expected value. The failing results were attributed to a transcription error in the sample weight. Exhibit 31, Investigation 05-011 was initiated on 10/7/05 when Hyoscyamine Sulfate Tablets, batch 5823A failed to meet specification for assay. The failing results were not recorded in the laboratory notebook (**Exhibit 22**) and the raw data from the original chromatographic run was not saved. Included as **Exhibit 32**, is the test method for Hyoscyamine Sulfate Tablets.

Discussion with Management:

All present at the closeout meeting agreed with this Observation. Mr. Shah explained that all data generated will be documented in laboratory notebooks and the firm has updated the OOS procedure QC-059: Investigation of Out-Of-Specification and Suspect Test Results, Revision # 10 (Draft) to require all analysts to run all chromatographic testing to completion unless an error is detected before a sample is run. **Exhibit 33** includes the previous Revisions #8 and # 9 and the new Revision # 10 Draft of procedure QC-059. Audit trails will be reviewed and all raw data will be required to be printed. Graphic Mode will be disabled and testing parameters will be saved and printed at the time of testing.

OBSERVATION 3

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically, there is no assurance that the Quality Unit can detect discrepancies in reports for which they are responsible. Data and reports reviewed and approved by the Quality Unit were not accurate and complete and did not adhere to established procedures. In addition, changes are not always documented in the change control system. For example:

a) A page was left blank in [redacted] between the original and repeat testing of Carisoprodal, Aspirin and Codeine Tablets, Batches 2020A, A1, 36-month stability samples and 3027A1, 12-month stability samples, for Codeine Phosphate Assay. The page was later written on by the Director of QC indicating why the previous results had been disqualified.

b) The Process Validation Report for Ursodiol Capsules USP 300 mg [redacted] dated 6/23/06, did not mention the OOS result received during the Content Uniformity testing of Batch 51083A.

c) The Process Validation Report for Hydroxyzine HCl USP 50 mg [redacted] dated 8/9/05, did not mention the OOS result received during the Blend Assay testing of Batch # 5519A.

d) The current inventory of the exhibit batch listed in [redacted] The exhibit batch fe[redacted] is the exhibit batch fe[redacted] Additionally, the results for bulk stability o[redacted] reflect that of the testing of finished packaged product and not that of the bulk (see Observation # 7)

e) The compression page of the batch record for Quinipril was changed to add a statement about timeframes and how to pack the blend. This change did not go through the change control system.

Reference: 21 CFR 211.22(d)

Supporting Evidence and Relevance:

3a) In reviewing the testing of Carisoprodal, Aspirin and Codeine Tablets, Batches 2020A, A1, 36-month stability samples and 3027A1, 12-month stability samples, for Codeine Phosphate Assay, I noted that the assay was re-run in its entirety due to "dirty check valves and a possible worn seal in HPLC Instrument 24" as stated in a "Note to File" dated 2/24/04 (**Exhibit 34**). A page was left blank in Laboratory Notebook # 605-06 between the original testing on 2/18/05 and the repeat testing on 2/23/05 (**Exhibit 35**, page 3 was skipped). The page was later written on by the Director of Quality Control on 2/24/05, stating that the original results were disqualified according to the memo to file. I explained that pages should not be skipped within a laboratory notebook for any reason and that it is the responsibility of the Quality Unit to ensure that this is not a regular practice.

3b) In reviewing the Process Validation Report for Ursodial USP 300 mg [redacted] dated 6/23/06 (**Exhibit 36**), I noted that the Conclusions and Observations section did not mention the OOS result received during the Content Uniformity testing of Batch 51083A (as discussed in Observation 2 a). Standard Operating Procedure # 0055 indicates that "upon completion of the required batches, the Quality Assurance Director, or his designee, will prepare a final Validation Report. This report will contain a specific conclusion and will include all data points collected." (**Exhibit 37**) In addition, while reviewing the batch record for Ursodial Capsules, USP 300 mg, Batch 51083A, there were seven instances in which the checked by boxes had not been filled out by a second operator (**Exhibit 38**). This batch record was reviewed and approved by the Quality Unit without noting the deficiencies. I explained that the Process Validation Report needs to include all deviations, investigations and OOS results associated with the validation batches in order to formulate any conclusion with respect to the process validation. Part of the problem was that the OOS results generated for this batch had not been investigated as OOS results as discussed in Observation 2 a.

3c) In reviewing the Process Validation Report for Hydroxyzine HCl USP 50 mg [redacted] dated 8/9/05, (**Exhibit 39**), I noted that the Conclusions and Observations section did not mention the OOS result received during the Blend Assay testing of Batch # 5519A (As discussed in Observation 4 b). As stated above, the final Validation Report is to include all data points collected. I again explained the importance of documenting all deviations, investigations and OOS results associated with the validation batches within the Process Validation Report.

3d) During my review of the CMC sections of [redacted] noted that the current inventory of the exhibit batch states [redacted] (**Exhibit 40**) The exhibit batch for [redacted] inquired as to why the batch number listed for the bulk hold time study was RBR-1661. Mr. Shah explained that Batch RBR-1661 is the exhibit batch for [redacted] and

a) No initial investigation was made into the out of specification Assay-1 result for Buspirone HCl 5mg Tablets Batch # 3144A, 24-month stability [redacted] when the result was obtained on 3/20/05. Assay-1 was repeated within the same chromatographic run. There was no documented investigation until 7/15/05 and retesting did not include a re-injection of the same sample vial.

b) No initial investigation was made into the out of specification result for the Left-Slope Blend Assay sample of Hydroxyzine HCl Tablets, 50 mg Batch # 5519A [redacted] when the result was obtained on 6/24/05. The analysis of the Left-Slope sample was repeated within the same chromatographic run. There was no documented investigation until 7/27/05 and retesting did not include a re-injection of the same sample vial.

c) No initial investigation was made for an out of specification assay result for Quinapril HCl and Hydrochlorothiazide Tablets, 10/12.5 mg, Batch # 4180A1, 12-month stabilit [redacted] when the result was obtained on 5/24/05. The analysis was repeated with new sample solutions within the same chromatographic run. There was no documented investigation until 7/22/05, which indicated that the sample solutions were prepared using the average tablet weight instead of twice the average tablet weight, which resulted in peak areas of approximately 50% of the standard response. This explanation should not have resulted in an OOS result. The investigation did not address the OOS result generated.

d) No initial investigation was made for an out of specification blend uniformity result for Oxycodone HCl Tablets, 15 mg, Batch # 5023A [redacted] when the result was obtained on 1/14/05. The analysis was repeated within the same chromatographic run. There was no documented investigation until 7/13/05.

e) No initial investigation was made for the out of specification result [redacted] for Sample 1-1 for pooled dissolution of Oxycodone and Acetaminophen Capsules Batch # 5259A, when the result was obtained on 4/14/05. An additional injection was made for Sample 1-1 within the same chromatographic run and was used in the calculations. The original result had not been invalidated and there was no documented investigation until 7/19/05.

Reference: 21 CFR 211.192

Supporting Evidence and Relevance:

4a) No initial investigation was made into the out of specification Assay-1 result for Buspirone HCl 5mg Tablets Batch # 3144A, 24-month stability [redacted] when the result was obtained on 3/20/05 (**Exhibit 24**). Assay-1 was repeated within the same chromatographic run as can be seen in the sequence on page 1 of **Exhibit 23**. There was no documented investigation until 7/15/05, and retesting did not include a re-injection of the same sample vial (**Exhibit 27**). The investigation consisted of a "Note to File", which explained that "examination of the autosampler vial showed the septum was not seated properly. This could give an errant injection..." I explained that because the investigation was not documented for four months, it would be difficult to identify the route cause. I indicated that the investigation should have been documented at the time. I also indicated that there is no reason that this result should not have been identified as an OOS result. I explained that whenever data is generated, even if a cause can be identified, the OOS procedure should be followed and an investigation should be initiated immediately.

4b) No initial investigation was made into the out of specification result for the Left-Slope Blend Assay sample of Hydroxyzine HCl Tablets, 50 mg Batch # 5519A [redacted] when the result was obtained on 6/24/05 (**Exhibit 44**). The original injection for Left-Slope Blend Assay was

Sample Number 012 in the sequence. The analysis of the Left-Slope sample was repeated within the same chromatographic run as Sample Number 024 (**Exhibit 45**), which was the only recorded value. There was no documented investigation until 7/27/05, and retesting did not include a re-injection of the same sample vial. The investigation consisted of a Note to File, which indicated "while examining the sample autosample vials, it was noted that the problem solution was hazy or turbid.....the errant data was disqualified, since the problem was due to analyst error in initially filtering the sample solution" (**Exhibit 46**). No explanation could be given as to why the original result was not treated as an OOS result and why no formal investigation was initiated when the result had been received. This was a process validation batch as can be seen by the QA Sample Submission Form (**Exhibit 47**).

Documentary Sample 359776 was collected for Hydroxyzine HCl Tablets, 50 mg Batch # 5519A during this inspection.

4c) No initial investigation was made for an out of specification assay result for Quinapril HCl and Hydrochlorothiazide Tablets, 10/12.5 mg, Batch # 4180A1, 12-month stability when the result was obtained on 5/24/05. The result for Hydrochlorothiazide % Assay [redacted] B#4180A1 30pk (**Exhibit 48**). The analysis for Assay-1 and Assay-2 (B#4180A1 30 pk) was repeated with new sample solutions within the same chromatographic run as shown in the sequence printout **Exhibit 49**. The original results were not documented in Laboratory Notebook 665-00 (**Exhibit 50**), nor had they been attached to the chromatographic data packet. There was no documented investigation ("Note to File") until 7/22/05 (**Exhibit 51**), which indicated that the sample solutions were prepared using the average tablet weight instead of twice the average tablet weight, which resulted in peak areas of approximately 50% of the standard response. This explanation should not have resulted in an OOS result. The OOS was not due only to a sample weight error. The investigation did not address the OOS result generated. No explanation could be provided for the high OOS result for this analysis, nor could one be provided to explain why an OOS investigation had not been immediately initiated.

4d) Two samples were run for "Left Column - Top Right" within the same chromatographic run in the blend uniformity testing of Oxycodone HCl Tablets, 15 mg, Batch # 5023A (**Exhibit 52**). No initial investigation was made for the first out of specification blend uniformity result [redacted] Oxycodone HCl for "Left Column - Top Right", when the result was obtained on 1/14/05 (**Exhibit 53**). The analysis was repeated within the same chromatographic run, with the second result falling within specification (**Exhibit 54**). A note in Laboratory Notebook # 1100-16 indicated that the sample for "Left Column - Top Right is re-injected because of higher result [redacted] which is comparatively higher than other sample. Re-injection is made from original sample comes out [redacted] (**Exhibit 55**). There was no documented investigation until 7/13/05, which consists of a "Note to File" (**Exhibit 56**). The investigation hypothesized that the sample autosampler vial might not have been capped correctly, but there was no documentation of such in the laboratory notebook. The original result had not been invalidated. I explained that an investigation should have been conducted immediately into the OOS results and that the original result should have been the result that was reported. There was no cause identified that would have invalidated the original results and retesting should not have been conducted without investigating the original result.

4e) No initial investigation was made for the out of specification result [redacted]r Sample 1-1 for pooled dissolution of Oxycodone and Acetaminophen Capsules Batch # 5259A, when the result was obtained on 4/14/05 (**Exhibit 10**). An additional injection was made for Sample 1-1 within the same chromatographic run and was used in the calculations. The sequence showing that two injections were made in the same run is attached as **Exhibit 9**. The original result had not been invalidated and there was no documented investigation until 7/19/05, which consisted of a "Note to File" (**Exhibit 13**). (Please see the discussion of Observation 2 b) I again explained the importance of immediately initiating investigations into OOS results.

Discussion with Management:

All present at the closeout meeting agreed with this observation. Mr. Shah explained that all data generated will be documented in laboratory notebooks and the firm has updated the OOS procedure QC-059: Investigation of Out-Of-Specification and Suspect Test Results, Revision # 10 (Draft) (**Exhibit 33**) to require all analysts to run all chromatographic testing to completion unless an error is detected before a sample is run. Audit trails will be reviewed and all raw data will be required to be printed. Graphic Mode will be disabled and testing parameters will be saved and printed at the time of testing. Mr. Shah also stated that when a retest is conducted a suffix or prefix will be added to the sequence name to indicate that this is not an original run and is in fact a re-test.

OBSERVATION 5

Input to and output from the computer are not checked for accuracy.

Specifically, audits were not conducted of the TotalChrom Data Acquisition System used to run the HPLC instruments during analysis of drug products. Sample injections, processing methods, and sample weights were not reviewed or verified for the accuracy of reported sample results during testing of in-process, finished product and stability samples.

Reference: 21 CFR 211.68(b)

Supporting Evidence and Relevance:

Electronic data files and laboratory notebooks were not reviewed for accuracy and authenticity by Laboratory Management. On numerous occasions laboratory management did not review the laboratory notebook and the electronic data files to ensure that all testing performed was reported and documented in the laboratory notebook. See FDA-483 observations 2 and 4.

Establishment Inspection Report	FEI:	2244683
Actavis Totowa LLC	EI Start:	07/10/2006
Little Falls, NJ 07424-5608	EI End:	08/10/2006

Discussion with Management:

Mr. Shah stated that audit trails will be reviewed and laboratory notebooks and HPLC data files will be reviewed to ensure that complete data is printed and documented.

OBSERVATION 6

The suitability of all testing methods is not verified under actual conditions of use.

Specifically, there is no assurance that equipment is adequately cleaned due to the deficiencies in cleaning validation studies. For example:

a) Cleaning validation was performed for the process trains of the following products without evaluating for sample recovery: Amidal Nasal Decongestant Tablets, Amigesic Caplets 750 mg, Carisoprodol and Aspirin Tablets USP 200 mg/325 mg, Carisoprodol Tablets USP 350 mg, Chlorzoxazone Tablets USP 250 mg and 500 mg, Digoxin Tablets USP 0.25 mg, Guanfacine Tablets USP 2 mg, Meperidine Hydrochloride Tablets USP 100 mg and 50 mg CII, Pemoline Tablets 75 mg CIV, Phentermine Hydrochloride Capsules USP 30 mg and 37.5 mg CIV, Ursodiol Capsules USP 300 mg. (This list is not all inclusive.)

b) Recovery studies were performed by applying a known amount of active pharmaceutical ingredient directly to a swab instead of applying the active to a coupon or template to replicate the equipment surface from which the active should have been swabbed. Cleaning validation was performed in this manner for the process trains of the following products: Buspirone Hydrochloride Tablets USP 5mg, 10 mg and 15 mg, Hydrocodone Bitartate and Homatropine Methylbromide Tablets 5mg/1.5mg, Mirtazapine Tablets 45 mg, Oxycodone and Acetaminophen Capsules USP 5 mg/500 mg, Oxycodone Hydrochloride Tablets USP 15 mg and 30 mg, Pemoline Tablets 18.75 mg CIV, Pentazocine Hydrochloride and Acetaminophen Tablets 25 mg (base) and 650 mg CIV, Quinaretic (Quinapril HCl and Hydrochlorthiazide Tablets) 20 mg/ 25 mg. (This list is not all inclusive.)

c) Cleaning Validation studies do not indicate whether or not a cleaning agent was used when cleaning the equipment process train. Equipment cleaning SOPs prior to March 2006 indicated that equipment could be cleaned "using hot water or with approved cleaning agent and water if necessary". In addition, there are no studies to show the cleaning agent is effectively removed from equipment during the cleaning process.

d) The method for [redacted] to analyze for residual active after the production of [redacted] although the method was not evaluated for specificity until 5/9/05.

Reference: 21 CFR 211.194(a)(2)

Supporting Evidence and Relevance:

6a) In reviewing cleaning validations for multiple products, I noted that prior to late 2004 or early 2005, recovery studies were either not performed at all or were performed by directly applying a known amount of API to a swab instead of using the swab to remove a known amount of API from a

template replicating the equipment. **Exhibit 57** shows that there was no testing of a swab for recovery in the Cleaning Validation Report for Amidal Tablets, Batch # 3024A. **Exhibit 58** shows that there was no testing of a swab for recovery in the Cleaning Validation Report for Digoxin Tablets, Batch # 8037A. Mr. Shah indicated that Digoxin is the most potent of drug products manufactured at the facility. I explained that it is particularly important that appropriate recovery studies be conducted for this drug product. A complete list of all products lacking recovery studies was provided and is attached as **Exhibit 59**.

6b) In reviewing the Cleaning Validation Report for Buspirone Hydrochloride Tablets, I noted that the recovery study was performed by adding 10.0 mL of 5 ppm std (Active Pharmaceutical Ingredient (API)) directly onto a cotton swab (**Exhibit 60**). I asked if the API had been applied to a template or a coupon, which would replicate the equipment surface, and then swabbed to show recovery capabilities. Mr. Shah indicated that this had not been done. I explained that applying the API directly to the swab does not effectively represent the ability of the cotton swab to remove the active from the manufacturing equipment. I also noted that recovery studies were performed in the same way (API applied directly to cotton swab) for Pentazocine HCl and Acetaminophen Caplets (**Exhibit 61**). Mr. Shah explained that Acetaminophen is the hardest to clean drug product due to its insolubility in water. A complete list of products where recovery studies were performed by adding the API directly to the cotton swab is attached as **Exhibit 62**.

6c) Cleaning Validation studies do not indicate whether or not a cleaning agent was used when cleaning the equipment process train prior to conducting the study. Equipment cleaning SOPs prior to March 2006 indicated that equipment could be cleaned "using hot water or with approved cleaning agent and water if necessary". DOI # PRD-012, Revision #02: Pony Mixer-Cleaning, dated 1/2/95, stated, "wash the mixer's blades using hot water or with approved cleaning agent and water if necessary" (**Exhibit 63**). DOI # PRD-012, Revision #03: Pony Mixer-Cleaning, dated 3/28/06, states, "wash the mixer's blades using approved cleaning agent and rinse the blades with hot water" (**Exhibit 64**). DOI # PRD-007, Revision #04: Blenders-Cleaning, dated 11/8/99 stated, "wash the internal surface and internal intake/discharge area(s) of the blender using hot water or with approved cleaning agent and water if needed" (**Exhibit 65**). DOI # PRD-007, Revision #05: Blenders-Cleaning, dated 3/28/06 states, "using a clean cloth soaked in approved cleaning solution (1 part cleaner to 3 parts water) hand wash the internal surface and internal intake/discharge area(s) of the blender" (**Exhibit 66**). Mr. Shah indicated that all cleaning validations and verifications were performed on equipment that had been cleaned using detergent. There are no studies to show the cleaning agent is effectively removed from equipment during the cleaning process. I explained the purpose of including detergent studies in the cleaning validations to ensure all detergent is adequately removed in the cleaning of equipment.

6d) The method for cleaning verification of [redacted] analyze for residual active after the production of [redacted] as shown by the laboratory notebook page, which indicates the start of analysis as 4/26/05 and completion on 4/28/05 (**Exhibit 67**) as well as the Cleaning Evaluation Document, dated 4/28/05 (**Exhibit 68**). However, the method was not evaluated for specificity until 5/9/05 as

shown on the coversheet of Data acquisition using [redacted] (Exhibit 69). I explained the importance of ensuring a method is validated prior to using the method for analysis.

Discussion with Management:

All present at the closeout meeting agreed with this Observation. Mr. Shah explained that all cleaning validations are to be included in a matrix approach, which will include appropriate recovery studies. He also explained that the matrix will include hardest to clean and most potent drug products. Mr. Shah stated that detergent studies were already initiated prior to the start of this inspection, but had not yet been completed.

OBSERVATION 7

The written stability testing program is not followed.

Specifically, the stability data recorded as that of bulk stability hold time studies are actually obtained from the testing of the following packaged finished products:

[redacted]

Buspirone Hydrochloride Tablets, USP 30 mg
Imipramine Hydrochloride Tablets, USP 10 mg, 25 mg, 50 mg
Methimazole Tablets, USP 5 mg, 10 mg
Phendimetrazine Tartrate Tablets, USP 35 mg

Reference: 21 CFR 211.166(a)

Supporting Evidence and Relevance:

In reviewing the inventory of [redacted] I noted that one bottle had been removed from inventory on 7/20/05, and a second bottle was removed from inventory on 10/19/05 (Exhibit 70). Mr. Shah indicated that these bottles had been taken by Quality Assurance and were sent to the QC Laboratory for analysis. When I inquired as to why these bottles had been pulled for testing when finished product testing had already been completed, Mr. Shah investigated and found that the two bottles had been mistakenly pulled for the bulk hold time stability testing. I asked how this happened and the response was that the Data Processor who enters the data and scheduling for products to be pulled for testing, did not have the option of typing "Bulk" under the "Stage" column (Exhibit 71). Instead, "Finished Product" had been selected for that field and the Quality Assurance Packaging Supervisor had pulled a bottle of finished product to

send to the laboratory for testing instead of sampling from the bulk material held for the bulk hold time stability studies. I asked what other finished products had been tested instead of bulk product to support bulk hold time stability studies. Mr. Shah provided a list (**Exhibit 72**), which included [redacted]

Discussion with Management:

All present at the closeout meeting agreed with this Observation. Mr. Shah explained that the "Stage" Field had been updated such that the Data Processor may now enter "Bulk Tablets" instead of "Finished Product" so that there is no confusion when the Quality Assurance Packaging Supervisor is pulling samples to submit to the laboratory (**Exhibit 73**). Mr. Shah indicated that all of the bulk hold time studies will be repeated on each of the above listed products. He explained that because the three-month and six-month time points have already passed, the bulk will be tested at this point and will be given a hold time of the number of months that have passed since its manufacture if all results are acceptable. **Exhibit 74** consists of the QA Sample Submission Forms that show the time points that will be tested for each of these products. If results are not acceptable, the hold time studies will be repeated at the three-month and six-month time points on future batches.

PRODUCTION SYSTEM

OBSERVATION 8

Examination and testing of samples is not done to assure that in-process materials conform to specifications.

Specifically, on numerous occasions quality assurance personnel failed to detect tablets and capsules which did not meet in-process specifications for tablet weight and thickness. SOP-016, "Routine Tablet Press Overcheck", requires a new set of samples be taken when out of specifications results are encountered, this did not occur. For example:

a) On 7/15/05, during the compression of Carisoprodal Tablets, Batch 5564A, one tablet was documented as having an out of specification value of 5.9 kp for hardness on the "QA In-Process Compression Overcheck Data Sheet". The hardness specification [redacted] The OOS tablet was discovered on 5/19/06, during the compilation of data for the Annual Product Review. Additional tablets were not tested as required by SOP QA-16 and no tablets were rejected which may have been required.

b) On 11/21/05, during the compression of Carisoprodol , Aspirin & Codeine Tablets, Batch 5904A, one tablet was documented as having an out of specification value of 8.9 kp for hardness on the "QA In-Process

Compression Overcheck Data Sheet", the hardness specification is [redacted]. The out of specification tablet was discovered on 4/26/06, during the compilation of data for the Annual Product Review. Additional tablets were not tested as required by SOP QA-16 and no tablets were rejected which may have been required.

c) On 8/13/05, during the compression of Quinaretic (Quinapril HCL and HCTZ) Tablets, Batch 5659A , one tablet was documented as having an out of specification hardness value of [redacted] on the "QA In-Process Compression Overcheck Data Sheet" the hardness specification is [redacted]. The out of specification tablet was discovered on 5/19/06, during the compilation of data for the Annual Product Review. Additional tablets were not tested as required by SOP QA-16 and no tablets were rejected which may have been required.

d) On 5/19/05, during the compression of Meclizine Hydrochloride Chewable Tablets, Batch 5352A, one tablet was documented as being out of specification for weight and no action was taken. The tablet weight was documented as [redacted] on the "QA In-Process Compression Overcheck Data Sheet" the weight specification is [redacted]. The out of specification tablet was not investigated until 12/08/05, when it was discovered during the compilation of data for the Annual Product Review. Therefore, additional tablets were not tested as required by SOP QA-16 and no tablets were rejected which may have been required.

e) On 8/16/05, during the compression of Phenazopyridine Hydrochloride Tablets, Batch 5678A, one tablet was documented as being out of specification for weight. The tablet weight was documented as [redacted] the "QA In-Process Compression Overcheck Data Sheet" and the weight specification is [redacted]. The out of specification tablet was not investigated until 6/16/06, when it was discovered during the compilation of data for the Annual Product Review. Therefore, additional tablets were not tested as required by SOP QA-16 and no tablets were rejected which may have been required.

Reference: 21 CFR 211.110(b)

Supporting Evidence and Relevance:

Please note: There was a typographical error in issuing 483 where Observation 8d and 8e were combined.

8a) **Exhibit 76,** Investigation # 06-027, for Carisoprodol Tablets, Batch 5564A shows that while compiling data for the annual product review, an out of specification tablet was documented by QA Inspectors on the "QA In-Process Compression Overcheck Data Sheet" **(Exhibit 76 page 6 & 7).** The QA Inspector did not take any action as required by Departmental Operating Instructions (DOI).

Exhibit 75, DOI # QA-016, "Routine Tablet Press Overcheck", states:

> "If any tablet run for hardness or thickness exceeds the above ranges run an additional set of tablets for the failing parameters only. If all values are within the range, the sample may be passed. If the range is still exceeded place the production back to the last QA check should be placed on Hold."

This procedure was not followed; no additional samples were collected and no product was rejected. There is no assurance that QA Operators can detect and document out of specification tablets.

8b) **Exhibit 77,** Investigation # 06-019, for Carisoprodol, Aspirin & Codeine Tablets, Batch 5904A, shows that while compiling data for the annual product review an out of specification tablet was documented on the "QA In-Process Compression Overcheck Data Sheet" **(Exhibit 77,** page

8). The QA Inspector did not take any action as required by Departmental Operating Instructions (DOI).

> **Exhibit 75**, DOI # QA-016, "Routine Tablet Press Overcheck", states:
> "If any tablet run for hardness or thickness exceeds the above ranges run an additional set of tablets for the failing parameters only. If all values are within the range, the sample may be passed . If the range is still exceeded place the production back to the last QA check should be placed on Hold."

This procedure was not followed; no additional samples were collected and no product was rejected. There is no assurance that QA Operators can detect and document out of specification tablets.

8c) **Exhibit 78,** Investigation # 06-028, for Quinaretic (Quinapril HCL and HCTZ) Tablets, Batch 5659A , shows that while compiling data for the annual product review an out of specification tablet was documented on the "QA In-Process Compression Overcheck Data Sheet" (Exhibit 78, page 9 &10). The QA Inspector did not take any action as required by Departmental Operating Instructions (DOI).

Exhibit 75, DOI # QA-016, "Routine Tablet Press Overcheck" states:

> "If any tablet run for hardness or thickness exceeds the above ranges run an additional set of tablets for the failing parameters only. If all values are within the range, the sample may be passed . If the range is still exceeded place the production back to the last QA check should be placed on Hold."

This procedure was not followed; no additional samples were collected and no product was rejected. **Exhibit 78,** page 9 & 10, the Compression Over Check Data Sheet also shows that an out of specification resul[redacted]was documented at 10:15 on 8/12/05 and was then change[redacted]hich is within specification. The overwrite from[redacted]s not dated and signed as required.

8d) **Exhibit 79,** Investigation # 05-014, for Meclizine Hydrochloride Chewable Tablets, Batch 5352A, shows that while compiling data for the annual product review, an out of specification tablet was documented on the "QA In-Process Compression Overcheck Data Sheet" (**Exhibit # 79, page** 9). The QA Inspector did not take any action as required by Departmental Operating Instructions (DOI).

Exhibit 75, DOI # QA-016, "Routine Tablet Press Overcheck" states:

> "If any tablet run for hardness or thickness exceeds the above ranges run an additional set of tablets for the failing parameters only. If all values are within the range, the sample may be passed . If the range is still exceeded place the production back to the last QA check should be placed on Hold."

This procedure was not followed; no additional samples were collected and no product was rejected. There is no assurance that QA Operators can detect and document out of specification tablets.

8e) **Exhibit 80**, Investigation # 06-038, for Phenazopyridine Hydrochloride Tablets, Batch 5678A, shows that while compiling data for the annual product review an out of specification tablet was documented on the "QA In-Process Compression Overcheck Data Sheet" (**Exhibit 81**). The QA Inspector did not take any action as required by Departmental Operating Instructions (DOI).

Exhibit 75, DOI # QA-016, "Routine Tablet Press Overcheck" states:

> "If any tablet run for hardness or thickness exceeds the above ranges run an additional set of tablets for the failing parameters only. If all values are within the range, the sample may be passed . If the range is still exceeded place the production back to the last QA check should be placed on Hold."

This procedure was not followed; no additional samples were collected and no product was rejected.

Discussion with Management:

All present at the closeout meeting agreed with this Observation. Mr. Shah explained that the standard operating procedure DOI # PRD-084: Tablet Press Operation, was updated to require that all failing results be documented and when out of specification tablets are found, the tablet press should be stopped immediately and production and quality should be notified. Additionally, the procedure requires that all findings need to be documented in the comments section of the compression data sheet. This procedure is in draft form and is attached as **Exhibit 82**.

OBSERVATION 9

Deviations from written production and process control procedures are not recorded and justified.

Specifically, there is no assurance that all manufacturing deviations are documented. For example:

a) On 11/8/05, Mirtazapine OD Tablets were observed to contain black specks during tablet inspection. Investigation 05-013, into the black specks states that during compression the operators observed the product sticking to the punch tips. The operator was instructed by the supervisor to remove and clean the upper and lower punches and then polish the punch tips. The dies and feed frame were also removed and cleaned. None of this was documented on the "Compression Data Sheet" which shows no problems were encountered in compression.

b) On 5/19/06, during the compression of Quinapril HCL Hydrochloprothiazide Tablets, Batch 60423A, tablets

were compressed below the action limit of 7.0 kp. The "Compression Data Sheet" does not indicate that there were any problems with compression although the entire Batch was compressed at a range of [redacted] which is below the target tablet hardness of [redacted] and below the action limit [redacted] investigation for this Batch was not initiated until 6/2/06 when the Batch did not meet yield specifications. The low yield was attributed to broken tablets.

c) Deviation 05-11 was generated when Pentazocine HCL & Naloxone HCL Tablets, Batch RBR2104 could not be compressed at the required tablet hardness specification o[redacted]n 4/27/05. Compression was stopped and a supplement was filed with FDA to change the hardness specification t[redacted]There is no "QA In-Process Compression Start Up Data Sheet" dated 4/27/06. The only compression start up sheet is dated 5/4/06 which is updated with the new tablet hardness specification of [redacted]

Reference: 21 CFR 211.100(b)

Supporting Evidence and Relevance:

There is no assurance that when problems are encountered in production, they will be documented. I explained the importance of documenting all problems in manufacturing at the time they occur, so that everyone is aware of problems that may impact on the quality of a drug product. Additionally, I stated that it was unacceptable to only document problems in an investigation that was initiated weeks after the deviation occurred.

9a) **Exhibit 83**, Investigation 05-013 was initiated on 11/9/05 when line operators observed Mirtazapine Tablets, Batch 5900A, contained black specks and smudge marks. Page 2 of the investigation, under the heading "Employee Interviews," it states that problems were encountered on 10/26/05, after about 10 minutes of running time. It was observed that the product was sticking to the punch tips. The operator was instructed by the supervisor to remove and clean the upper and lower punches and then polish the punch tips. The machine and tooling were then checked for cleanliness by the Supervisor and QA reassembled. The product continued sticking to the punches throughout the remainder of compression.

Exhibit 84, the "Compression Data Sheet" for Mirtazapine, Batch 5900A, shows that compression started up at 10:00 AM. The line was approved for start-up by QA and ten tablets were checked every 30 minutes throughout compression for tablet appearance, weight, hardness and thickness, which were all within specification. The only time the log shows the equipment was stopped was at 11:40 for lunch and at 1:28 PM for break. The log has nothing filled out in the comments section about product sticking or the supervisors instructions to break down the equipment and clean and no documentation to show that there were any problems with compression. **Exhibit 85**, the "Compression Tooling Cleaning and Usage Log", also does not show any additional cleaning of the compression equipment.

9b) There is no assurance that operators are capable of detecting tablets that do not meet internal action limits. **Exhibit 86**, Investigation 6-030, was initiated on 6/2/06, when the percent yield after inspection of film coated tablets did not meet specification. The low yield was attributed to broken tablets. The operators found 10.26 kg of waste after inspection which is approximately 50,220

tablets. The investigation states that operators were having trouble achieving the target hardness value of 9.0 and notified the supervisor. My review of the compression Batch record for Quinapril HCL Hydrochloprothiazide Tablets, Batch 60423A, did not reveal any documentation stating that operators were having trouble achieving the target hardness value [redacted] **Exhibit 87,** shows the entire lot was compressed on 5/19/06, with tablet hardness values [redacted] all tablets were outside the action limit of [redacted] The operators did not take any action to bring the tablet hardness into the target range. The "Compression Data Sheet" has nothing filled out in the comments section about any problems achieving the target value for hardness or about compressing tablets outside the action limit. There is no documentation to show that operators tried to adjust the tablet hardness or that they notified a supervisor. The compression log shows that compression was started at 8:15 am and was approved by QA, although the tablets did not meet the target tablet hardness or the action limit. Every [redacted] throughout compression, [redacted] were checked for weight, appearance, thickness and hardness without any noted problems or any action being taken.

9c) There is no assurance that operators document all compression start-up activities. I reviewed deviation report # 05-011, **(Exhibit 89)** which was issued when Pentazocine and Naloxone Hydrochloride Tablets, Batch RBR2104, could not be compressed at the specified hardness range of [redacted] The deviation report is dated 4/29/05. When I requested the Batch record, I noted that the compression data sheet in the Batch record was dated 5/4/05, one week after the deviation report was generated. I asked how the deviation report was generated in April when the Batch was not compressed until 5/4/05, per the Batch record. I was told that the Batch was initially compressed on 4/29/05, but that the tablet hardness specification could not be achieved. There is no documentation to show that out of specification tablets were compressed on 4/29/06. I requested to see the original "Compression Data Sheet" from 4/29/05, and I was told that there was no sheet for that date. I explained to firm management that the compression sheet should have been issued and filled out with at least the header information and the start-up data showing that tablet hardness could not be achieved. **Exhibit 90,** the "Equipment Usage and Cleaning Log" shows that when Pentazocine and Naloxone Hydrochloride Tablets, Batch RBR2104 was started in compression on 4/27/06, and was completed on 5/4/06.

Discussion with Management:

All present at the closeout agreed with this Observation. Mr. Shah stated that DOI PRD-122: Batch Record Data Entry was updated to require that non-routine occurrences or out of specification results be properly documented. This SOP is currently in Draft form and is attached as **Exhibit 91.**

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OBSERVATION 10

The master production and control records are deficient in that they do not include complete sampling and procedures.

There is no assurance that all in-process blend samples collected from the mixer are 1 x 3 times the tablet/capsule weight as required. The sample collection is not documented and the sample weight is not measured. For example:

The QA submission form, which is submitted to the laboratory with the in-process blend uniformity samples, does not include the sample weights and the collection of the samples is not recorded in the Batch record.

Reference: 21 CFR 211.186(b)(9)

Supporting Evidence and Relevance:

There is no assurance that all blend samples collected are 1 x 3 times the capsule weight as required by the firm's procedures.

All validation and finished blend samples collected are required to be 1 X 3 times the capsule or tablet weight as demonstrated by the Ispadipine Capsules Validation Protocol (Exhibit 92). Included as **Exhibit 93**, are "QA Sample Submission Forms" which do not require that blend sample weights be documented. **Included as Exhibit 94**, is an example of a completed "QA Sample Submission Form." Sample weight is determined by the cavity size that is used in the sample thief. **Exhibit 95**, a sample label that would be used to label in-process blend samples shows that sample weight is not recorded.

Discussion with Management:

All present for the closeout meeting agreed with this Observation. During the inspection the label for the in-process blend sample was updated to require the addition of sample weight to the label (**Exhibit 96**). Additionally, all sample collectors were instructed to start taking and recording sample weights. Mr. Shah explained that change control forms were submitted requesting a change to specify that the blend sample should be as close to, but should not exceed 3 times the dosage unit weight (**Exhibit 97**).

FACILITIES & EQUIPMENT SYSTEM

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OBSERVATION 11

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically, equipment qualifications are deficient in that acceptance criteria are not specified, and discrepancies are not documented. For example:

a) The Re-Qualification of the [redacted] which was used in the production of [redacted] does not have clearly defined acceptance criteria. In addition, there is no discrepancy report to explain why equipment drawings, equipment schematics, equipment manuals and purchase orders were not available, what steps had been taken in an attempt to obtain these materials and why this was acceptable.

b) The specified utility requirements were not met in the equipment re-qualification for [redacted] was used in the production of [redacted] The specification for voltage was 220 Volts, but the actual voltage is 208 Volts. There is no discrepancy report to explain why this failure to meet the specification is or is not acceptable.

c) There are no equipment qualifications for the [redacted] These ovens are used in the production of [redacted] as well as more than fifteen other products.

Reference: 21 CFR 211.63

Supporting Evidence and Relevance:

11a) In reviewing the Re-Qualification of the [redacted] which was used in the production of [redacted] it was noted that the Installation Qualification and Operational Qualification do not have clearly defined acceptance criteria (**Exhibit 98, page 1**). There is no discrepancy report to explain why equipment drawings, equipment schematics, equipment manuals and purchase orders were not available, what steps had been taken in an attempt to obtain these materials and why this was acceptable (**Exhibit 98, page 2**). There was no acceptance criteria identified for RPM of the Tablet Press running at low and high speeds, results were simply recorded (**Exhibit 98, page 3**). In addition, no placebo Batch was run at high and low speeds and high and low hardness as was done in other, previous tablet press qualifications. When I asked as to why no placebo Batch had been evaluated, the response was that this was only a Re-Qualification of the Equipment ID #70. I asked for the original Qualification, dated 9/28/98, which consisted of one page that only identified the equipment (**Exhibit 99**). I explained that the original Qualification was inadequate. Tablet Press # 70 is used in the production of approximately 15 other products, which are listed in **Exhibit 100**. I discussed the importance of including specific acceptance criteria in order to verify that equipment is appropriate for its intended

use. I also explained that when criteria is not met, the discrepancy should be appropriately documented and evaluated.

11b) The specified utility requirements were not met in the equipment [redacted] which was used in the production of [redacted]. The specification for voltage was 220 Volts, but the actual voltage is 208 Volts (**Exhibit 101, page 1**). There is no discrepancy report to explain why this failure to meet the specification is or is not acceptable (**Exhibit 101, page 2**). In addition, I noted that while reviewing the Equipment Re-Qualification Protocol for Fitzmill ID #12, there were two pages in the protocol for [redacted] (**Exhibit 101, pages 3-4**). These incorrect pages were not noted by any of the individuals who conducted, reviewed or approved the Re-Qualification. The same was noted in the Equipment Re-Qualification Protocol for Fitzmill ID #11; pages had also been swapped.

11c) There are no equipment qualifications for the [redacted] 1 or the [redacted] These ovens are used in the production of [redacted] as well as more than fifteen other products **Exhibit 100**. I explained the importance of ensuring that all pieces of major equipment used in the production of drug products are qualified.

Discussion with Management:

All present at the closeout meeting agreed with this Observation. Mr. Shah explained that all equipment qualifications will be assessed for adequacy and qualifications will be repeated where necessary.

OBSERVATION 12

Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically, there is no assurance that preventative maintenance is conducted for equipment at scheduled intervals. For example:

a) Duct tape was observed on the feed throat of [redacted] during the tour of manufacturing operations.

b) There are no preventative maintenance programs for the [redacted]

c) Preventative Maintenance is to be conducted on [redacted] every six months according to DOI # PRD-011: Blenders - Preventative Maintenance and Repairs." However, no maintenance had been conducted between 1/8/04 and 12/8/04 or between 5/12/05 and 5/19/06.

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Reference: 21 CFR 211.67(b)

Supporting Evidence and Relevance:

12a) While touring the production area, I noted that [redacted] large piece of duct tape attached across the feed throat of the piece of equipment. No explanation could be provided for the use of the tape other than it probably prevented powder from escaping through the feed throat during production. The use of duct tape on production equipment is not an authorized practice. I indicated that if material was escaping from the feed throat during equipment use, then the equipment should have been evaluated to see what was needed to fix this problem (i.e. replacing a gasket or tightening the closure to the feed throat). This should have been addressed through the maintenance program for this piece of equipment.

12b) There are no preventive maintenance programs for the [redacted] I inquired as to how there was an "Equipment Preventive Maintenance and Repair Log" for Drying over #271 without having a preventive maintenance program. No explanation could be provided. The log documented the replacement of the heating element and motor, replacement of the motor fan belt, replacement of the recording pin arm, etc. (**Exhibit 102**). I indicated all of these items should be evaluated as part of a preventive maintenance program.

12c) Preventive Maintenance is to be conducted on Double Cone Blender ID # 41 every six months according to DOI # PRD-011: Blenders - Preventative Maintenance and Repairs" (**Exhibit 103**). However, no maintenance had been conducted between 1/8/04 and 12/8/04 or between 5/12/05 and 5/19/06 according to the "Equipment Preventive Maintenance and Repair Log" for Equipment ID # 41 (**Exhibit 104**). In addition, I noted that when the preventive maintenance was recorded in the log, the description of the work performed states "checked steps 1-3". According to the procedure, steps 2 and 3 are not applicable to this particular blender. I explained that it is important to specify what steps are actually taken instead of documenting actions that can't even be performed on this particular piece of equipment. I also explained the importance of following established preventive maintenance programs. Blender # 41 is used in the production of products listed in **Exhibit 105**.

Discussion with Management:

All present at the closeout meeting agreed with this Observation. Mr. Shah explained that all procedures for calibration and preventive maintenance were reviewed prior to the closeout meeting. A new SOP is in place for DOI PRD-249: Drying Ovens – Preventive Maintenance and Repairs, Effective 7/26/06 (**Exhibit 106**). In addition, a new SOP is in draft for DOI PRD-011: Blenders – Preventive Maintenace & Repairs, describing how to perform and document preventive maintenance and repairs for blenders (**Exhibit 107**).

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MATERIALS SYSTEM

OBSERVATION 13

Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacturing or processing operations for which they are unsuitable.

Specifically, rejected Batches are not labeled as rejected or placed in a section of the warehouse for rejected products. For example:

a) Acetaminophen/Caffeine/Dihydrocodeine/Bitrartrate Tablets, Batch RBR2526 was rejected on 3/17/06, when the final blend uniformity samples failed to meet specifications. On 7/13/06, this Batch was not labeled as rejected and was in the WIP (work in progress) Warehouse, labeled as "In-Process".

b) Cyclobenzaprine HCL Tablets, Batch 5846 was rejected on 10/7/05, when blend uniformity samples failed to meet specifications. On 7/13/06, this Batch was not labeled "rejected" and was found in the WIP (work in progress) warehouse, labeled as "In-Process".

c) Dantrolene Sodium Capsules, Batches 60220A, 60228A and 60229A, were rejected on 5/17/06, when final blend uniformity samples failed to meet specifications. On 7/13/06, this Batch was not labeled as rejected when it was found in the in the WIP (work in progress) Warehouse.

Reference: 21 CFR 211.110(d)

Supporting Evidence and Relevance:

13a) **Exhibit 109**, Investigation # 06-012, shows that Acetaminophen/Caffeine/Dihydrocodeine /Bitrartrate Tablets, Batch RBR 2526 failed to meet specification for blend uniformity and was rejected on 3/29/06. On 7/13/06, I requested to see the destruction notice for the Batch and I was told it had not been destroyed yet. I then requested to see the Batch. The Batch was located in the middle of the work in-process warehouse labeled as "In-Process." Included as **Exhibit 110**, is a photocopy of the drum label, taken on 7/13/06. **Exhibit 108**, QA-002, "Rejecting an Item" requires materials to be labeled with the appropriate status.

13b) **Exhibit 111**, Investigation # 05-012, shows that Cyclobenzaprine HCl Tablets, Batch 5846A, failed to meet specifications for blend uniformity and was rejected on 12/15/05. On 7/13/06, I requested the destruction notice for the lot and that the lot had not been destroyed yet. I then requested to see the lot, which was found in the middle of the work in-process warehouse labeled as

"In-Process." Included as **Exhibit 112**, is a photocopy of the drum label on 7/13/06. **Exhibit #** 108, QA-002, "Rejecting an Item" requires materials to be labeled with the appropriate status.

13c) **Exhibit 113**, Investigation # 06-016, shows that Dantrolene Batches 60220A, 60228A and 60229A, failed to meet dissolution specifications and were rejected on 5/17/06. On 7/13/06, I requested to see the destruction notice for the lot and I was told the lot had not been destroyed yet. I requested to see the lot which was in the work in-process warehouse and was not labeled as "Rejected." The batches were at the filled polish capsules stage and were labeled as "Quarantine" awaiting release testing (**exhibit 114**).

Discussion with Management:

All present at the closeout meeting agreed with this Observation. Mr. Jasmine Shah and Mr. D. Patel explained that they were very concerned that rejected product was not labeled as such. Mr. Shah instructed that rejected materials be labeled correctly and that the status of other rejected products be checked. Mr. Shah and Mr. Ashok, stated that all employees had been reminded about placing rejected materials in the correct status. Departmental Operating Instructions DOI QA-002 Rejecting an Item, was updated to include timeframes for hold/rejection status and for placing the rejected stickers on the product. Mr. Shah provided a copy of the procedure, which was approved on 7/24/06, and is attached as Exhibit # 116.

OBSERVATION 14

Written procedures are not followed for the receipt and storage of components.

Specifically, all locations are not identified throughout the warehouse as required by Departmental Operating Instructions (DOI) PRD-068: "Raw Material Locator System", nor are they recorded on Material Inventory Cards as required by DOI PRD-066: "Receiving Raw Materials & Packaging Components," to describe where materials are located in the warehouse. For example:

a) Magnesium Hydroxide PO # 60875 was observed in the warehouse in an unidentified location. There was no location filled out on the Material Inventory Card.
b) Unitab Microcrystalline Cellulose PO # 60134-6 was observed in the warehouse in an unidentified location. There was no location filled out on the Material Inventory Card.

Reference: 21 CFR 211.80(a)

Supporting Evidence and Relevance:
In touring the warehouse and reviewing Material Inventory Cards, I noted that locations were not identified throughout the warehouse as required by Departmental Operating Instructions (DOI)

PRD-068: "Raw Material Locator System" (**Exhibit 117**). When I referred to the Material Inventory Cards for items located in areas that were unidentified, I noted that the Location # had been left blank as well instead of being recorded as required by DOI PRD-066: "Receiving Raw Materials & Packaging Components" (**Exhibit 118**). Magnesium Hydroxide PO # 60875 was observed in the warehouse in an unidentified location. There was no location filled out on the Material Inventory Card (**Exhibit 119**). Unitab Microcrystalline Cellulose PO # 60134-6 was observed in the warehouse in an unidentified location. There was no location filled out on the Material Inventory Card (**Exhibit 120**). I explained the importance of identifying all locations in the warehouse so that materials can be easily located by the appropriate personnel. I discussed the importance of following all warehousing SOPs in order to prevent mix-ups and to maintain control of material movement.

Discussion with Management:
All present at the closeout meeting agreed with this Observation. Measures have been taken in order to identify all locations within the warehouse and to record locations on the Material Inventory Cards.

OBSERVATION 15

There was a failure to handle and store components at all times in a manner to prevent contamination.

Specifically, all raw materials for a Batch are weighed in the manufacturing room without cleaning between the dispensing of each ingredient. The cleaning log for the room only reflects the cleaning of the room after the production of the Batch. In addition, procedures do not indicate that the active ingredient should be the last material to be weighed.

Reference: 21 CFR 211.80(b)

Supporting Evidence and Relevance:
In touring the production area, I noted that materials are dispensed within the manufacturing suite. Mr. Shah indicated that there were no rooms specifically designated for the dispensing of raw materials and that it was a regular practice to weigh out all raw materials in the manufacturing rooms in the order in which they appear in the manufacturing Batch record. I noted that this order does not allow for the active pharmaceutical ingredient to be weighed last. In addition, the cleaning log for the room only reflects the cleaning of the room after the production of the Batch. I explained that there is a concern for potential cross-contamination between the different raw materials through the weighing of all materials in the same room without performing a cleaning each ingredient. I discussed the importance of performing at least a dry cleaning between the dispensing of each raw

material and weighing the active pharmaceutical ingredient last to prevent any contamination of excipients dispensed within the same suite.

Discussion with Management:
All present at the closeout meeting agreed with this Observation. Mr. Shah provided an updated procedure, DOI # PRD-247: Operating Instructions for Weighing Raw Materials to be Used in Pharmaceutical Production **(Exhibit 121)**, which states that inactive ingredients are to be weighed first, one at a time, active ingredients are to be weighed last and a dry cleaning is to take place between the dispensing of each ingredient. Mr. Shah also explained that the new facility on 900 Riverview Drive, Totowa, NJ has specifically designated dispensing rooms for future production operations.

REFUSALS

There were no refusals throughout the course of this inspection.

GENERAL DISCUSSION WITH MANAGEMENT

The following items were discussed both during the inspection and again at the closeout meeting.

Labeling of glassware:
During the tour of the analytical laboratory, I noted that in several instances, glassware containing test solutions and preparations were not identified with a product name and Batch number. I explained the importance of properly identifying all laboratory glassware in order to prevent mix-ups. Prior to the close of the inspection, Mr. Shah provided a copy of a new procedure, DOI: QC-157: Labeling of Standard/Sample Solution Vessels, dated 7/19/06 **(Exhibit # 122)**. He explained that all laboratory personnel were to be trained in the new procedure immediately.

Stability of Solutions:
In reviewing cleaning validation studies, I noted that there was a trend in which the equipment would be swabbed, but the analysis of the swabs would not take place until five or ten days later. I exlained that data needs to be available to support the time that the swabs are sitting in solution prior to analysis, or the analysis should take place within the timeframe in which the solutions have

already been shown to be stable. Mr. Shah explained that when the matrix cleaning validation is completed, the swabs will be taken to the laboratory and immediately analyzed.

SAMPLES COLLECTED

Documentary Sample #359776, which demonstrates the interstate shipment of Hydroxyzine Hydrochloride Tablets, USP 50 mg, Batch # 5519A, was collected during the course of this inspection.

ATTACHMENTS

FDA 482, dated 7/10/06, 1 page
FDA 482, dated 7/12/06, 1 page
FDA 483, dated 8/10/06, 9 pages

EXHIBITS COLLECTED

1) Labeling for all products manufactured at Actavis Totowa, LLC, Little Falls, NJ, 167 pages
2) Floor Plan, Little Falls, 1 page
3) Product List, 2 pages
4) Organizational Chart, 1 page
5) List of Quality Control personnel, 2 pages

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6) OOS Investigation # 06-001, Ursodiol 300mg Capsules, Batch 51083A; dated 1/11/06, 24 pages
7) Ursodiol Capsules, Laboratory Notebook # 12-00-32, 8 pages
8) Laboratory Method for Ursodiol Capsules, 22 pages
9) Chromatographic sequence for Oxycodone and Acetaminophen Capsules Batch # 5259A showing two injections for Sample 1-1, 1 page
10) Original results for Oxycodone and Acetaminophen Capsules Batch # 5259A Sample 1-1, 1 page

11) Laboratory Notebook # 700-34, dissolution release testing of Oxycodone and Acetaminophen Capsules Batch # 5259A, 5 pages
12) Re-test results for Oxycodone and Acetaminophen Capsules Batch # 5259A Sample 1-1, 1 page
13) Note to File, dated 7/19/05, for Batch # 5259A, 2 pages
14) Chromatographic sequence for Amidrine Capsules, Batch # 5637A, showing two injections for Capsule-2, 1 page
15) Original result for Amidrine Capsules, Batch # 5637A Capsule-2, 1 page
16) Laboratory Notebook # 349-08, dissolution testing of Amidrine Capsules, Batch # 5637A, 5 pages
17) Re-test results for Amidrine Capsules, Batch # 5637A Capsule-2, 1 page
18) Note to File, dated 8/12/05, for Batch # 5637A, 2 pages
19) Investigation # 06-029, Quinapril HCl & Hydrochlorothiazide Tablets, Batch 60423A, 11 pages
20) TotalChrom Data Acquisition worksheets for Quinapril HCl Tablets, Batch 60423A, 70 pages
21) Laboratory Test Method & Notebook for Quinapril HCl & Hydrochlorothiazide Tablets, 31 pages
22) Laboratory Notebook and testing data for Hyoscyamine Sulfate Tablets 0.125 mg SL, 41 pages
23) Chromatographic sequence and chromatograms for assay analysis of Buspirone HCl 5 mg Tablets Batch # 3144A, 24 month stability, showing two injections for Assay-1(3144A-500 Pack) 4 pages.
24) Original result for Assay-1(3144A-500 Pack) Buspirone HCl 5 mg Tablets Batch # 3144A, 1 page.
25) Laboratory Notebook # 666-01, Assay and Impurity testing of Buspirone HCl 5 mg Tablets Batch # 3144A, 5 pages
26) Re-test results for Assay-1 (Exhibit 26) (3144A-500 Pack) Buspirone HCl 5 mg Tablets Batch # 3144A, 1 page.
27) Note to File, dated 7/15/05, for Batch # 3144A, 2 pages
28) Chromatographic sequence and chromatograms for assay testing of Amidrine Capsules Batch # 5113A, showing two injections for Assay-1, 3 pages
29) Laboratory Notebook # 349-07, Assay testing of Amidrine Capsules Batch # 5113A, 5 pages
30) Note to File, dated 7/18/05, for Batch # 5113A, 2 pages
31) Investigation # 05-011, Hyoscyamine Sulfate Tablets 0.125 mg SL, 1 page
32) La Laboratory Test Method for Hyoscyamine Sulfate Tablets 0.125 mg SL, 14 pages
33) Revisions # 8, # 9 and # 10, procedure QC-059: Investigation of Out-of-Specification and Suspect Test Results, 34 pages

FDA 483, Observation 3
34) Note to File, dated 2/24/04, for Batches # 2020A, A1 and Batch # 3027A1, 2 pages

35) Laboratory Notebook # 605-06 original and repeat testing of Carisoprodal, Aspirin and Codeine Tablets, Batches 2020A, A1, 36-month stability samples and 3027A1, 12-month stability samples, for Codeine Phosphate Assay, 6 pages
36) Process Validation Report for Ursodial USP 300 mg, 2 pages
37) Standard Operating Procedure # 0055, 1 page
38) Batch record for Ursodial Capsules, USP 300 mg, Batch 51083A, 1 page
39) Process Validation Report for Hydroxyzine HCl Tablets USP 50 mg, 2 pages
40) [redacted]
41) Investigation # 05-002, Quinapril HCl Hydrochlorothiazide Tablets, Batch 5341A, 24 pages
42) Quinapril HCl Hydrochlorothiazide Tablets, Compression Data Sheet, dated 5/16/06, 8 page.
43) Quinapril HCl Hydrochlorothiazide Tablets, Compression Data Sheet, dated 6/6/06, 22 pages

FDA 483, Observation 4
44) Original results for Blend Assay of Hydroxyzine HCl Tablets, 50 mg Batch # 5519A, 1 page
45) Re-test results for Blend Assay of Hydroxyzine HCl Tablets, 50 mg Batch # 5519A, 1 page
46) Note to File, dated 7/27/05, for Batch # 5519A, 2 pages
47) QA Sample Submission Form for Hydroxyzine HCl Tablets, 50 mg Batch # 5519A 1 page
48) Original results for Hydrochlorothiazide Assay of Quinapril HCl and Hydrochlorothiazide Tablets, 10/12.5 mg, Batch # 4180A1, 12-month stability, 1 page
49) Chromatographic sequence printout showing the analysis for Assay-1 and Assay-2 (B#4180A1 30 pk) was repeated within the same chromatographic run, 1 page
50) Laboratory Notebook 665-00, Assay testing of Quinapril HCl and Hydrochlorothiazide Tablets, 10/12.5 mg, Batch # 4180A1, 12-month stability, 4 pages
51) Note to File, dated 7/22/05, for Batch # 4180A1, A, 2 pages
52) Chromatographic sequence printout showing the analysis for "Left Column - Top Right" was repeated within the same chromatographic run in the blend uniformity testing of Oxycodone HCl Tablets, 15 mg, Batch # 5023A, 1 page
53) Original blend uniformity results for Oxycodone HCl Tablets Batch # 5023A, 1 page
54) Re-test blend uniformity results for Oxycodone HCl Tablets Batch # 5023A, 1 page
55) Laboratory Notebook # 1100-16, blend uniformity testing for Oxycodone HCl Tablets Batch # 5023A, 4 pages
56) Note to File, dated 7/13/05, for Batch # 5023A, 2 pages

FDA 483, Observation 6
57) Cleaning Validation Report for Amidal Tablets, Batch # 3024A, 1 page
58) Cleaning Validation Report for Digoxin Tablets, Batch # 8037A, 1 page
59) List of all products lacking recovery studies, 1 page
60) Cleaning Validation Report for Buspirone Hydrochloride Tablets, 1 page
61) Cleaning Validation Report for Pentazocine HCl and Acetaminophen Caplets, 1 page
62) List of products where recovery studies were performed by adding the API directly to the cotton swab, 1 page
63) DOI # PRD-012, Revision #02: Pony Mixer-Cleaning, dated 1/2/95, 2 pages
64) DOI # PRD-012, Revision #03: Pony Mixer-Cleaning, dated 3/28/06, 3 pages
65) DOI # PRD-007, Revision #04: Blenders-Cleaning, dated 11/8/99, 2 pages

66) DOI # PRD-007, Revision #05: Blenders-Cleaning, dated 3/28/06, 3 pages
67) Laboratory Notebook, cleaning verification of Benztropine Mesylate RBR-2136 and RBR-2137, 1 page
68) Cleaning Evaluation Document for Benztropine Mesylate RBR-2136 and RBR-2137, 2 pages
69) Coversheet of Data acquisition using Turbochrom C/S system showing evaluation of method for specificity, 1 page

FDA 483, Observation 7
70) Inventory record for [redacted] Exhibit Batch RBR-2137, 1 page
71) Example of scheduling for products to be pulled for testing issued by a Data Processor, 1 page
72) List of products affected by bulk hold time tablet samples pulled from packaged bottles, 1 page
73) Updated example of scheduling for products to be pulled for testing issued by a Data Processor, 1 page
74) QA Sample Submission Forms, 10 pages

FDA 483, Observation 8
75) DOI # QA-016, Routine Tablet Press Overcheck, 2 pages
76) Investigation # 06-027, Carisoprodol 350 mg Tablets, Batch # 5564A, 8 pages
77) Investigation # 06-019, Carisoprodol, Aspirin & Codeine Phosphate Tablets, Batch # 5904A, 8 pages
78) Investigation # 06-028, Quinaretic (Quinapril HCL and HCTZ Tablets) Batch # 5659A, 10 pages
79) Investigation # 05-014, Meclizine Hydrochloride Chewable Tablets, Batch # 5352A, 9 pages
80) Investigation # 06-038, Phenazopyridine Hydrochloride Tablets, Batch # 5678A, 10 pages
81) QA In-Process Compression Overcheck Data Sheets, 1 page.
82) DOI # PRD-084: Tablet Press Operation, 7 pages

FDA 483, Observation 9
83) Investigation # 05-013, Mirtazapine OD Tablets, Batch # 5900A, 6 pages
84) Compression Data Sheet for Mirtazapine OD Tablets, Batch # 5900A, 2 pages
85) Compression Tooling Cleaning and Usage Log, 2 pages
86) Investigation # 06-030, Quinapril HCl & Hydrochlorothiazide Tablets, Batch 60423A, 3 pages
87) Compression Data Sheet for Quinapril HCl & HCTZ Tablets, Batch 60423A, 4 pages
88) QA In-Process Sampling and Testing Program - Quinapril HCl & HCTZ Tablets, 4 pages
89) Deviation Report # 05-011, Pentazocine and Naloxone Hydrochloride Tablets, Batch RBR2104, 3 pages
90) Compression Data Sheet, Pentazocine and Naloxone Hydrochloride Tablets, Batch RBR2104
Equipment Usage and Cleaning Log for Stokes Tablet Press, 5 pages
91) DOI PRD-122: Batch Record Data Entry, 3 pages

FDA 483, Observation 10
92) Isradipine Capsules, Process Validation Protocol, 2 pages
93) QA Sample Submission Form, 2 pages
94) QA Sample Submission Form, Completed, 2 pages
95) In-Process blend sample label, 1 page
96) Updated, in-process blend sample label, 1 page
97) Change Control Request Form, 4 pages

FDA 483, Observation 11
98) Re-Qualification of the [redacted] Equipment ID # 70, 3 pages
99) Original Qualification of the [redacted] Equipment ID # 70, 1 page
100) List of products that utilize the Drying Ovens and Tablet Press # 70, 1 page
101) Re-qualification fo[redacted]2, 4 pages

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102) Equipment Preventive Maintenance and Repair Log for Drying over #271, 1 page
103) DOI # PRD-011: Blenders - Preventative Maintenance and Repairs, 1 page
104) Equipment Preventive Maintenance and Repair Log for Equipment ID # 41, 1 page
105) List of products that utilize Blender # 41, 1 page
106) DOI PRD-249: Drying Ovens – Preventive Maintenance and Repairs, 2 pages
107) DOI PRD-011: Blenders – Preventive Maintenace & Repairs, 4 pages

FDA 483, Observation 13
108) DOI#: QA-002 Rev. 05, Rejecting an Item; revision 05, 4 pages
109) Investigation # 06-012, APAP/Caffeine/Dihydrocodeine/Bitrartrate Tablets, Batch RBR2526, 11 pages
110) Bulk Drum Label from APAP/Caffeine/Dihydrocodeine/Bitrartrate Tablets, Batch RBR2526, 1 page
111) Investigation # 05-012, Cyclobenzaprine HCl Tablets, Batch 5846A, 9 pages
112) Bulk Drum Label from Cyclobenzaprine HCl Tablets, Batch 5846A, 2 pages
113) Investigation # 06-016, Dantrolene Sodium Capsules, lot 60220A, 60228A and 60229A, 16 pages
114) Bulk Drum Label from Dantrolene Sodium Capsules, lot 60220A, 60228A and 60229A, 1 page
115) Revised, DOI#: QA-002 Rev. 06, Rejecting an Item, 3 pages
116) Revised, DOI#: QA-002 Rev. 06, Rejecting an Item, 5 pages

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117) DOI PRD-068: Raw Material Locator System, 2 pages
118) DOI PRD-066: Receiving Raw Materials & Packaging Components, 2 pages
119) Material Inventory Card for Magnesium Hydroxide PO # 60875, 1 page
120) Material Inventory Card for Unitab Microcrystalline Cellulose PO # 60134-6, 1 page

Establishment Inspection Report	FEI:	2244683
Actavis Totowa LLC	EI Start:	07/10/2006
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121) DOI # PRD-247: Operating Instructions for Weighing Raw Materials to be Used in Pharmaceutical Production, 3 pages

122) DOI: QC-157: Labeling of Standard/Sample Solution Vessels, dated 7/19/06, 2 pages

RELEASE

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C.O. DATE

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